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HEMATOPOIETIC RECOVERY
IN IRRADIATED DOGS

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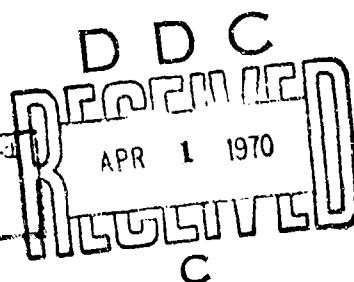
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HEMATOPOIETIC RECOVERY IN IRRADIATED DOGS

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ACKNOWLEDGMENT

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FOREWORD
(Nontechnical summary)

It is known that up to radiation exposures which will kill many animals, it is injury to the blood-forming tissue which causes radiation disease. In the rodent it has been observed that hematological recovery occurs in an oscillatory manner. However, precise data for larger animals are not available.

This study was designed to measure hematological recovery in dogs, a larger mammal, exposed once or repeatedly to either 150 rads of x rays or 150 rads of mixed gamma-neutron radiation. Comparisons were made among animals exposed to each radiation quality and to different numbers of repeated exposures.

Prior to the first exposure, on the day of irradiation as well as on a number of days postirradiation, several hematological tests were made on all dogs. It was found that immediately after irradiation dogs show an initial decrease in the production of red cells followed by an oscillatory recovery response during the subsequent 30 days postirradiation. Near complete recovery noted on days 5 and 11 was followed by cellular decreases reaching low values about days 6 and 18. Postirradiation periodicity was also noted for white cells and platelets albeit to a lesser degree.

In general, for a given dose, the effects of x rays were significantly greater than those of the mixed gamma-neutron radiation. This was particularly pronounced in the number of lethalities with repeated radiation exposures.

Previously irradiated dogs did not respond as well to a subsequent exposure of equal magnitude after a 3-month rest period. This clearly implicated residual injury to blood stem cells from the last radiation exposure.

Since the oscillatory recovery responses in the dogs were similar to those observed previously in rodents, they may be basic response patterns in mammals. Presumably hematological response mechanisms have their origin in the inherent negative feedback systems of blood cell production.

ABSTRACT

Hematological recovery in dogs exposed once or repeatedly to either 150 rads of x rays or 150 rads of mixed gamma-neutron radiation was measured. Comparisons were made among animals exposed to each radiation quality and to different numbers of repeated exposures.

Prior to the first radiation exposure, on the day of irradiation, as well as on days 1 to 12, 15, 18, 21, 24, 27 and 30 postirradiation, hematological values were obtained from all dogs. These included ^{59}Fe incorporation, erythrocyte and plasma volume determinations, plasma iron concentration and clearance, hematocrits, total as well as differential peripheral leukocyte and platelet counts.

Immediately after irradiation, all dogs showed an initial decrease in erythropoietic values followed by an oscillatory recovery response during the subsequent 30 days postirradiation. Near complete recovery on days 5 and 11 was followed by cellular decreases reaching low values about days 6 and 18. Postirradiation periodicity was also noted for leukocytes and platelets albeit to a lesser degree.

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Previously irradiated dogs did not respond as well to a subsequent exposure of equal magnitude alter a 3-month rest period. This clearly implicated residual injury in stem cells from the prior radiation exposure.

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Presumably these hematological response mechanisms have their origin in the inherent negative feedback systems of hematopoiesis.

I. INTRODUCTION

It has been clearly established that the number of newly formed erythrocytes in the rat oscillates during the first two weeks of recovery after sublethal irradiation.[5,22] Fluctuations are also suspected for leukocytes.[11] Recently, similar recovery responses have been reported for mice.[23] Since radiation-induced disease and deaths up to midlethal exposures are primarily caused by injury to the hematopoietic system, it is important to establish early hematological recovery trends. However, precise data for larger animals are not available.

The objectives of the present study were to measure hematological recovery responses in the sublethally irradiated dog exposed to 150 rads of x rays; and, furthermore, to compare these effects with those observed in animals irradiated with 150 rads of mixed gamma-neutron radiation. Finally, measurements of hematological recovery capabilities were to be obtained in previously irradiated dogs subjected to subsequent identical exposures after 3-month intervals.

II. METHODS

Healthy, purebred, AKC registrable beagles, 1 to 2 years of age were utilized in this study. The dogs were bred and boarded at the colony of Richard E. Saunders, Inc., Richmond, Virginia. They were under a veterinarian's care for the elimination of parasite infestation and immunization against distemper, hepatitis and rabies.

Three weeks prior to experimentation, the dogs were transferred to temperature-controlled rooms at the Armed Forces Radiobiology Research Institute (AFRRI). They were maintained individually in stainless steel cages, fed kibbled laboratory dog

food supplemented once a week with high protein canned meat ration. Water was provided ad libitum.

A total of 252 dogs was utilized in this study; 114 were subjected to 150 rads of x rays, another 114 to 150 rads of mixed gamma-neutron radiation and 24 served as unirradiated controls. One month prior to the first radiation exposure, hematological base-line control values were obtained from all dogs. These included ^{59}Fe incorporation into newly formed erythrocytes, erythrocyte and plasma volume determinations, plasma iron concentration and clearance, hematocrits, total as well as differential peripheral leukocyte, and platelet counts per mm^3 of blood.

On the day of radiation exposure as well as on days 1 to 12, 15, 18, 21, 24, 27 and 30 postirradiation, the hematological values described above were obtained from six dogs in each radiation group. These experimental values were also obtained from six unirradiated control dogs on days 1, 9, 18 and 27 postirradiation for comparison with base-line values obtained from irradiated animals before the initial exposure. In addition, hematocrits, total and differential leukocyte and platelet counts were also measured on days 13, 14, 16, 17, 19, 22, 25, 28, 31, 34, 37, 45 and 86 after radiation exposure.

Due to limited housing facilities at the AFRRI, the experiments were actually conducted with 42 dogs at a time. This permitted the utilization of one dog per radiation group and day of observation as delineated above. After six identical replications over an 18-month period using 42 animals each time, the total number of 252 dogs was employed. Furthermore, this resulted in the use of six dogs per day of study as listed above for each radiation group and the controls.

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After a 90-day postirradiation period during which the hematological tests were conducted, the dogs were irradiated for the second time. This procedure was used as a test for residual injury. The animals were irradiated for the third and final time 90 days later. All hematological tests conducted after the first radiation exposure were repeated after the second and third exposures.

A radial beam generator was utilized as the x-ray source. It has the following physical factors: 250 kVp, 30 mA, 1.2 mm Be + 0.95 mm Cu filtration (HVL - 1.9 mm Cu); and target to subject midline distance 105 cm. The absorbed dose rate at the center of the dogs was 20 rads/min. Dosimetry techniques were published previously.[15] For the x-ray exposures, the dogs were placed in Plexiglas containers and arranged in a circle at equidistance from the radiation source. The exposure rate varied less than 8 percent from one end to the other of the container midline.

The AFRRI-TRIGA reactor was the source for the mixed gamma-neutron radiation. The description of the exposure room and radiation field has been published earlier.[14] The dogs were placed in the exposure room so that they were in a radiation field with an isodose surface 292 cm from the reactor center line. The midline tissue dose rate, as measured in a small unperturbed tissue sample which was in charged-particle equilibrium and surrounded by air, was 20 rads/min; the ratio of gamma to neutron kermas was 1.5. The effective gamma energy was between 1 and 2 MeV. The procedures for dosimetry have been published previously.[9]

Bilateral exposure conditions were achieved at both radiation sources by securing the exposure boxes to turntables and rotating them 180° at half exposure time. Depth-dose measurements conducted earlier[15] indicated that the exposures were Class A as defined in ICRU Report 10e.[20]

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On the days of study as listed above, the dogs were first injected via the left jugular vein with 1 ml of a sodium citrate-buffered $FeCl_3$ solution containing 25 μCi of ^{59}Fe in 0.25 μg of total iron. Next, they received 1 ml of Evans blue (T-1824) which contained 4.5 mg of the anhydrous salt. During the next hour, three 3-ml blood samples were removed from the right jugular vein at 20-minute intervals. The ^{59}Fe clearance time and the T-1824 plasma volume were determined from these samples. Seven days later a blood sample was withdrawn from the dogs and the ^{59}Fe incorporation was determined. The radioactivity of 250 μl of this blood sample was counted in an automatic dual-channel, well-type, gamma scintillation detector using a 3 x 3 thallium-activated sodium iodide crystal. To determine the total radioiron activity in the blood, a blood volume was determined from independent measurements of the red cell and plasma volumes.

The method described by Sterling and Gray[26] using ^{51}Cr labeled erythrocytes was used for red cell volume determination. Since the blood of all dogs also contained ^{59}Fe labeled cells, the dual-channel gamma scintillation detector was used to differentiate this isotopic gamma activity from that of the ^{51}Cr. One channel with a 0.1 V window was adjusted to the ^{51}Cr photopeak energy and the other with a 70 V window to the ^{59}Fe peak. The Compton tail from the ^{59}Fe spectrum also contributed to the ^{51}Cr reading. A correction for this contribution was obtained in the following manner. A blood sample containing ^{59}Fe labeled cells was obtained from the jugular vein of each dog, 250 μl of which was counted on both channels. Thereafter, 1 ml of ^{51}Cr labeled erythrocytes was injected intravenously. A small sample of blood was withdrawn 15 minutes later, 250 μl of this sample were counted using the above described narrow

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window. The activity counted by the narrow window setting prior to the injection of ^{51}Cr labeled cells was deducted from that after their injection. This value was the true radioactive count from the ^{51}Cr.

Plasma iron concentrations were obtained using the method of Caraway.[13] Since the activity of the injected ^{59}Fe decreased exponentially, the $T_{1/2}$ was determined from the calculated slope. The plasma iron turnover per day was calculated utilizing the method described by Huff et al.[19]

Hematocrits were measured by the standard microhematocrit method. A Coulter counter was used for total leukocyte counts. Neutrophil and lymphocyte concentrations were obtained by multiplying the fraction of each cell type determined from differential smears by the total white cell count per mm^3 of blood. Platelets were counted by the phase-contrast method of Brecher and Cronkite.[12]

To determine the significance of the effects with repeated radiation exposures, a "t" test of the difference between two means for correlated observation was utilized.[28]

III. RESULTS

Immediately after x irradiation, dogs show a 30 percent decrease in ^{59}Fe incorporation when compared with their own preirradiation control values (Figure 1A). This decrease persists for the next 3 days. Increases are noted for the 4th and 5th postirradiation days with a maximum return in radioiron uptake to 90 percent of control values. A secondary decrease occurs thereafter with a low value of 50 percent on the 6th day. A second attempt toward recovery is noted between the 7th and 11th days after exposure, reaching a maximum of 96 percent. A third and final decrease

begins on the 12th day with a nadir of 62 percent on the 18th day. Final recovery commences from then on, with an apparent return to normal values by day 30.

Animals subjected to mixed gamma-neutron irradiation show an immediate post-irradiation decrease in ^{59}Fe uptake to 85 percent of normal. Further decreases to below 60 percent are noted on the following 2 days. An abortive rise begins on the 3rd day with a maximum of 90 percent of control values on the 5th day. A secondary decrease follows with low points of 73 percent from control values on the 7th and 8th days after exposure. A second recovery attempt is observed for the next 3 days with a return to normal values on days 10 and 11. The last descent in iron uptake values is noted thereafter, with a final low point at day 18. However, the low values never decrease below 82 percent. From then on a gradual return to normalcy is indicated.

Comparing the effect of the two radiation qualities, it is seen that the initial depression is significantly more severe for the mixed gamma-neutron radiation after the first day postirradiation. However, the first abortive recovery is similar for both groups. The second and third decreases in ^{59}Fe uptake are significantly greater in x irradiated dogs, the second recovery reaches a higher zenith in those exposed to mixed gamma-neutron radiation. Final recovery to normal values is obtained by both exposure groups on the 30th day.

Erythropoietic recovery in dogs exposed for a second time to 150 rads of x rays or mixed gamma-neutron radiation after a 3-month interval shows a similarity to that observed after one dose of radiation (Figure 1B). However, recovery responses are less efficient. There are again signs that the ^{59}Fe uptake during the first two days is depressed further in gamma-neutron exposed dogs. However, the first abortive rise

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is much more successful in this group of animals (90 percent γ-n versus 67 percent x rays). The second and third erythropoietic minima are significantly lower for the x irradiated group. Beyond the 5th postirradiation day the lowest iron uptake value for x irradiated dogs is 43 percent (day 6), whereas that of the reactor exposed group is 62 percent (day 7). Erythropoiesis is significantly lower from the 11th to the 27th day in x irradiated dogs. Recovery on the 30th postirradiation day appears to be similar for both exposure groups, however, neither has returned to normalcy.

In general, when comparing the effects of the two radiation sources upon erythropoiesis in dogs exposed for the second time, it is noted that those of x rays were significantly greater. This seems to be supported by the data from Table I which shows a sixfold greater mortality in this exposure group.

After the third radiation exposure, the erythropoietic recovery responses appear to be more irregular (Figure 1C). However, the initial depression and the abortive rise are still similar to those observed after earlier exposures. Again, the first ^{59}Fe depression is greater for γ-n irradiated animals and in turn they appear to recover better. On a comparison basis there is no question that x rays depressed iron uptake significantly further and retarded recovery. After the final exposure this condition might have been more aggravated since results from x irradiated dogs represent data from presumably healthier survivors. As may be noted from Table I, 41 out of 114 x irradiated animals were dead after the third exposure, whereas only 9 reactor exposed dogs became fatalities from an equally sized group.

As may be seen in Figure 2A, ^{59}Fe uptakes are significantly further depressed and recovery is retarded after each repeated exposure to x rays. On the other hand,
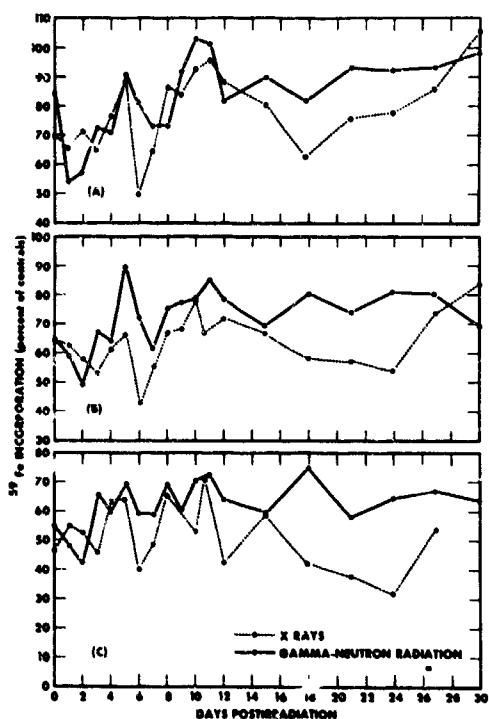
Figure 1. Postirradiation radioiron incorpora-
tion in dogs exposed to 150 rads x rays or
mixed gamma-neutron radiation.
(A) one exposure
(B) two exposures (3-month interval)
(C) three exposures (two 3-month intervals)
Each point represents the mean value of the
group.

Table I. Survival in Dogs Exposed Repeatedly to
X Rays or Gamma-Neutron Radiation

Number of repeated exposures	X ray*	Gamma-neutron radiation*
1	3/114	2/114
2	17/114	3/114
3	41/114	9/114

* Number of deaths/number per group before first exposure

similarities of oscillations in terms of depression in erythropoiesis and abortive or
unsuccessful recovery attempts are noted. Figure 2B shows data from dogs subjected
to mixed gamma-neutron radiation. Here again significant residual injury is noted
after each repeated exposure. Similarities in trends of decreases in ^{59}Fe uptake and
subsequent recovery attempts are indicated.

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A decrease in the number of platelets per mm^3 of blood is noted after exposure to either x rays or mixed gamma-neutron radiation (Figure 9). A low point is reached approximately 10 days later which persists until approximately the 25th postirradiation day for dogs exposed to either quality of radiation. Fluctuations in numbers of platelets are seen throughout this period of depression. This is followed by recovery and a return to apparent normalcy between the 45th and 86th day after exposure in dogs subjected to one or two doses of radiation. A possible retardation in recovery is indicated after the third exposure. Equal damage was inflicted upon platelets of the dogs exposed to either radiation source.
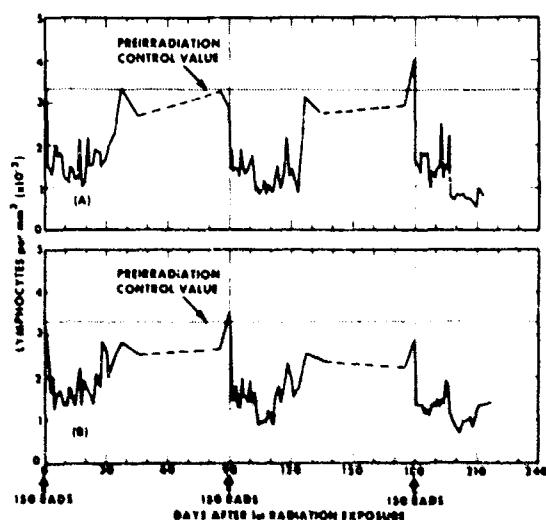

Figure 1. Postirradiation values of
lymphocytes in dogs.
(A) three exposures to x rays
(B) three exposures to gamma-neutron
radiation
Each point represents the mean value
of the group.
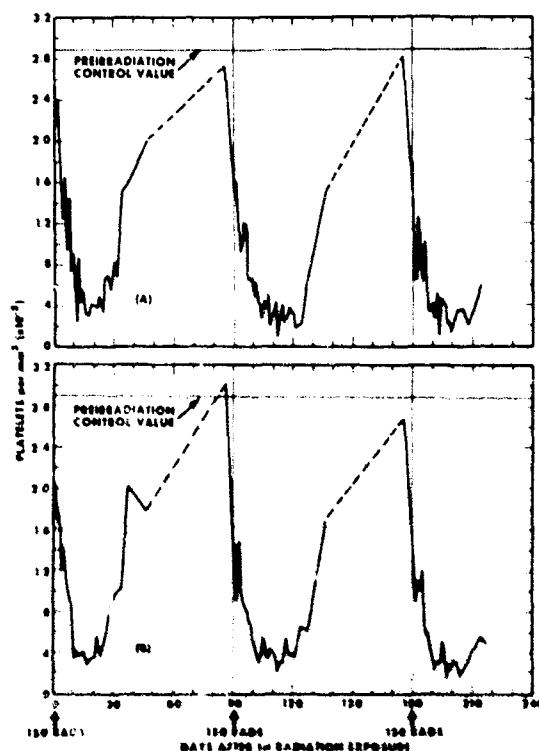
Figure 9. Postirradiation platelet values
in dogs.
(A) three exposures to x rays
(B) three exposures to gamma-neutron
radiation
Each point represents the mean value of
the group.

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IV. DISCUSSION

The present study clearly demonstrates oscillations in postirradiation erythro-
poietic recovery in the dog. Since this is similar to what had been reported for rod-
ents,[5,22,23] it appears to be the pattern of recovery in mammals. Interpretations
for this response mechanism vary greatly. Earlier investigators[2,11] were primarily
intrigued with the initial, also called abortive, response observed in rodents, and
postulated that it was caused by radiation injured stem cells capable of heteromor-
phogenic but not homomorphogenic division. This is particularly plausible for eryth-
rocytes since differentiation into and maintenance of the final functional adult cell
accounts for only a small fraction of the total information contained within the DNA of
any progenitor cell.[1] However, if the first rise in the number of cells is part of the
total oscillatory recovery pattern, then its cause must be much more complex and
most likely has its origin in the inherent negative feedback system.

Recently, it has been suggested that the bone marrow stem cell and the eryth-
rocytic system can be broken down into two feedback loops.[21,24] The first loop is
concerned with regenerative proliferation of the stem cells and is under the control
of a mitotic inhibitor or chalone, which is produced in proportion to the number of
stem cells. Increase in chalone concentration initiated by increased homomorphogenic
stem cell proliferation in response to radiation injury would in turn inhibit the latter
and cause periodicity in cellular production. Superimposed upon the fluctuations in
available stem cell numbers are the actions imposed on the erythrocytic system by
erythropoietin (loop 2), particularly in its control of the release of stem cells.[17]
The interaction of these two systems results in oscillations in the number of available

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stem cells and functional red cells. It has been further suggested that stressful perturbations of the bone marrow as caused by ionizing radiation may initiate a pulse stimulus acting on a basic oscillatory system.[23]

Values obtained for circulatory leukocytes and platelets in the dog appear to indicate oscillations in cellular numbers during their period of depression after radiation. Since blood samples were obtained at approximately the same time each day, diurnal variations cannot be implicated. The possibility exists, therefore, that interactions of the red cell feedback system, and those responsible for the formation of the other blood cells with the stem cells are responsible for the periodicity in blood cell numbers during the postirradiation period.

However, it is difficult to assess if competition for common stem cells contributes to the fluctuations in erythropoietic recovery. If such competition exists it appears to favor erythrocyte over leukocyte production.[18] Nevertheless, in the irradiated rat it was observed that leukopoietic recovery commenced at the time the first abortive rise for erythropoiesis terminated and secondary cellular decreases ensued.[9] The possibility of competition for common stem cells was considered. No evidence for this exists in the dog. Leukopoietic recovery begins long after several oscillations in erythropoiesis.

Periodicity in postirradiation cellular levels stresses the importance of frequent hematological testing during this period. Temporary higher readings obtained by infrequent tests might be misleading as to the true physiological condition of the system.

Although the present experiment was not designed to determine the RBE of the mixed gamma-neutron radiation employed, it permits a comparison of the effects of 150 rads from either source upon the hematological system as well as upon survival with repeated exposures at 3-month intervals. It appears to be quite clear that in all instances 250 kVp x rays caused significantly greater damage to the hematopoietic system. This is particularly pronounced for erythropoiesis after each repeated exposure. In previous reports,[3,8,10,15] it was suggested that the RBE of neutrons for bone marrow effects in dogs was between 0.8 and 1.0. This seems to support the greater effects of x rays on the hematopoietic system in the present study. Depth-dose studies in beagle phantoms exposed to either one of the radiation sources employed indicate Class A exposures.[15] It must be pointed out, however, that gamma radiation comprised 60 percent of the mixed radiation source and it is known from studies in rodents that it is absorbed to a lesser extent by the bone marrow as compared with x rays.[27]

Survival data after repeated exposures are much more impressive. Dogs subjected twice to gamma-neutron irradiation had a 3 percent mortality as against 15 percent for the x irradiated; whereas, after three repeated exposures, 8 percent of the exposed dogs succumbed to the former radiation quality, in comparison with 36 percent to the latter. Presumably, death in these dogs was caused by infection and insufficient protection by reduced numbers of leukocytes. However, the peripheral leukocytic values show only small, albeit significant, further decreases with repeated exposures. This might imply that once leukocytic values have reached a specific low threshold, additional relatively smaller decreases might well result in lethality.

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The data of the present study show unequivocally that dogs which had been previously exposed to 150 rads from either radiation source have a decreased capability to recover from a repeated dose of the same magnitude. An earlier study[8] indicated residual injury on the 5th postirradiation day in mongrel dogs exposed repeatedly to 150 rads of either x or neutron radiation. Since only one postirradiation day was studied, the results could have been obtained fortuitously due to the oscillatory nature of hematological recovery. However, the results of the present experiment with data from 19 days during a 30-day study leave no doubt that previously irradiated dogs accumulated residual injury. Since residual injury in the postirradiation hematopoietic system has been described for rodents[4,6,7] one might conjecture that this might well be common to mammals in general.

Residual injury in the context of the present report implies reduced capability for hematological recovery induced by a repeated sublethal dose of radiation of equal size. Presumably, this would only be elicited by other hematological stresses such as bleeding if they approach in magnitude those of a second radiation dose. Previously irradiated dogs could indeed respond well to hemorrhage as seen in the experiment by Perman et al.[25] as long as the reduced primitive progenitor pool can respond to the stress and produce the necessary number of cells. Apparently the stress of bleeding exceeded this capability in the postirradiated rats described in the report of Gong et al.,[16] since these authors were able to show an approximate 20 percent residual injury of the erythropoietic system 60 weeks after a sublethal radiation exposure. It must be postulated, therefore, that residual injury becomes apparent only if there is greater demand for erythropoiesis on the somewhat reduced stem cell pool vis-a-vis

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its capability to respond. It is quite clear that a second dose of radiation affecting the total hematological system would be able to demonstrate better the existing physical or physiological impairments of the stem cell system.

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13. ABSTRACT

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Prior to the first radiation exposure, on the day of irradiation, as well as on days 1 to 12, 15, 18, 21, 24, 27 and 30 postirradiation, hematological values were obtained from all dogs. These included ^{59}Fe incorporation, erythrocyte and plasma volume determinations, plasma iron concentration and clearance, hematocrits, total as well as differential peripheral leukocyte and platelet counts.

Immediately after irradiation, all dogs showed an initial decrease in erythropoietic values followed by an oscillatory recovery response during the subsequent 30 days postirradiation. Near complete recovery on days 5 and 11 was followed by cellular decreases reaching low values about days 6 and 18. Postirradiation periodicity was also noted for leukocytes and platelets albeit to a lesser degree.

In general, for a given dose, the effects of x rays were significantly greater than those of the mixed gamma-neutron radiation. This was particularly pronounced in the number of lethalities with repeated radiation exposures.

Previously irradiated dogs did not respond as well to a subsequent exposure of equal magnitude after a 3-month rest period. This clearly implicated residual injury in stem cells from the prior radiation exposure.

Since the oscillatory recovery responses in the dogs were similar to those observed previously in rodents, they may be basic response patterns in mammals. Presumably these hematological response mechanisms have their origin in the inherent negative feedback systems of hematopoiesis.

14. KEY WORDS	LINK A		LINK B		LINK C	
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